APPLIED

1.	*XIENCE V Everolimus Eluting Coronary Stent System Coating Process Performance Qualification Report*, at p. 4("ABT177200") ("The XIENCE V EECSS is a ML VISION stent coated with a PBMA primer layer and a drug/polymer matrix layer containing Everolimus and PVDF-HFP. Once the coating is applied, primer layer or the drug/polymer layer, the stent is dried and weighed prior to processing to the next process.").
2.	*Memorandum from Nadine Ding, Advisor, Product Development, to CR205039 – Increase the Primer Weight Range*, at p. 1 (ABT0283878) ("The drug layer of the XIENCE V system consists of PVDF-HFP and everolimus. It is applied separately over the already oven dried primer layer.").
3.	*Abbott Xience PMA Module 3* at § 5.3 (ABT0316406) ("The stent surface is prepared for coating, and then a PBMA primer layer and the PVDF-HFP drug matrix layer are applied to the stent via a spray-coating process.").
4.	*FDA Executive Summary Memorandum*, at p. 4 (ABT0601621) ("The drug matrix layer of PVDF-HFP and everolimus is applied to the stent at a drug loading of 100 $\mu g/cm^2$.").
5.	*Abbott Xience PMA Module 2* at § 3.2.A.3.S.3. (ABT311813) ("Upon coating, and drying, the PVDF-HFP polymer then crystallizes to its equilibrium level as it forms the drug reservoir matrix.").

XIENCE™ V Everolimus Eluting Coronary Stent System
Coating Process Performance Qualification Report

Author: Maria Stearn
Date: March 8, 2006

Approvals

Maria Stearn, Quality Engineer	3-8-06 Date
Frank De Meo, Quality Engineer Statistician	3-8-06 Date
Brandon Yoe, Process Engineer	3/9/06 Date
Juliet Manalili, Quality Engineering Manager	3-9-06 Date
Robert Dutchik, Manufacturing Engineer Manager	3/9/06 Date

Table of Contents: **Page:**

PURPOSE:

The purpose of this Performance Qualification is to provide a high degree of assurance that the processes impacting the primer and drug/polymer coating on the XIENCE™ V EECSS per XLHRBM1009551 consistently produce product that meets the finished product drug and coating specifications for release rate, total content, residual solvent, purity, coating integrity, BHT and particulates per PS1011002 required by DOP205.

SCOPE:

This Performance Qualification is applicable to the XIENCE™ V EECSS in diameters 2.5 – 4.0 mm and lengths 8 – 28 mm. For bracketing purposes, the small stent design and the medium stent design were grouped separately. The corner sizes for the small stent design are 2.5 x 8mm and 3.0 x 28mm and the corner sizes for the medium stent design are 3.5 x 8mm and 4.0 x 28mm. The 8mm stent represents one corner due to the lowest total drug load, resulting in worse case potential analytical method variation. The 28mm represents the opposite corner since it possesses the most coating surface area resulting in worse case potential for analytical method variation and coating damage. 18mm stents were built and tested in both the small and medium stent designs as an intermediate size.

The scope of this validation was limited to the processes that may affect coating; the processes include primer spraying, drug spraying, stent retention, pre-sterile packaging, sterilization and post-sterilization packaging.

Conclusion:

The coating performance qualification demonstrated with confidence and reliability that the processes impacting the coating met the specifications for release rate, total content, residual solvent, purity, coating integrity, particulates and BHT as defined in PS1011002 under nominal operating conditions.

BACKGROUND:

The XIENCE™ V EECSS is a ML VISION stent coated with a PBMA primer layer and a drug/polymer matrix layer containing Everolimus and PVDF-HFP. Once the coating is applied, primer layer or the drug/polymer layer, the stent is dried and weighed prior to processing to the next process. Once the final drug/polymer layer is dried, the XIENCE™ V coated stent is secured onto a balloon catheter using a stent retention process. The stent delivery system is then packaged, EtO sterilized and then secondary packaged prior to finished device testing and product release.

DEVIATIONS TO THE PROTOCOL: (reference page 38 for summary of deviations in Attachment II)

SAMPLE SIZE DETERMINATION:

Table 1 outlines the key analytical output characteristics to be tested. It also details the respective data type (attribute or variable) to be collected, the product sizes, lots and minimum samples to be built; where and how data will be collected and the minimum samples size chosen.

Sample sizes were based on the need to demonstrate the specified confidence and reliability levels for each key output characteristic. Sizes have been combined where there is no difference in product dimensions or processing, based on design and length. For example, Group 1 is comprised of small stent design at 8mm in length, reference column "Product Sizes to be Tested".

The number of lots for each characteristic is based on the sources of variability that would be expected to affect that characteristic. A minimum number of three lots are required to encompass normal manufacturing variability.

Memorandum

To: CR2050639 – Increase the Primer Weight Range

From: Nadine Ding, Advisor, Product Development 4/3/06

Date: April 3, 2006

Re: No Impact to FG Coating Quality, Drug Total Content, BHT Content or Purity

---

Summary

This justification relates to widening primer coat weight range by shifting the target coating weight upwards 20-40%. Such a change would not impact the drug total content, BHT content, or purity of the XIENCE™ V Everolimus Eluting Coronary Stent System.

Proposed Coating Thickness Change

In the XIENCE™ V system, PBMA is used as a primer to improve the coating adhesion to the stent's metal surface. Adhesion between the PBMA primer and Cr-Co metal is through monolayer van der Waals interactions at the interface. Increasing the primer weight adds additional layers of the primer coating. Additional layers of PBMA primer neither change the adhesion to the metal nor the interface to the drug layer.

The drug layer of the XIENCE™ V system consists of PVDF-HFP and everolimus. It is applied separately over the already oven dried primer layer. Atomic Force Microscopy measurements have shown that distinct drug coat and primer coat layers exist (Microstructural Analysis of Drug Eluting Stent, Shellie Rigby-Singleton of Molecular Profiles, 12 May 2005.)

Drug purity is determined mainly by the manufacturing process for the coating application and subsequent treatments (environmental exposures, etc.) It is not related to, nor impacted by, the chemically non-reactive primer layer underneath the drug layer.

Total drug content and BHT content are controlled by the drug coat weight applied and the subsequent manufacturing processes. Increase of primer thickness would have no impact on the drug content.

Conclusion

Increase of primer coat weight 20-40% will not affect the finished good properties of drug total content, BHT content, and purity.

42A

SUMMARY OF ALL CMC CHANGES

In the final PMA module for the XIENCE™ V Everolimus Eluting Coronary Stent System (M060008), the updates to the CMC section previously provided in Module 2 are summarized below:

Drug Substance

A detailed summary of the pertinent changes and/or new information for the Drug Substance sections is as follows:

3.2.S.7 Updated QOS and Section 3.2.S.7 in the main body of the current module. Added stability data tables of the formal stability study for two lots of drug substance in Container Closure II (4 grams per container) to present the 6 and 9-month results. Added stability data table of the formal stability study for one lot of drug substance in Container Closure II (18 grams per container) to include the 6-month results.

Drug Product

A detailed summary of the pertinent changes and/or new information for XIENCE™ V EECSS Drug Product is as follows:

3.2.P.2 Updated Section 3.2.P.2.2.2 Overages to correct Table 3.2.P.2-25 Historical and Proposed In-Process Coating Weight Targets and Total Content Results as stated in G050050/S056 (5/11/07).
Updated Section 3.2.P.2.4 Container Closure System to include a justification for the implementation of an electronic instructions for use (eIFU), remove references to the paper instructions for use (IFU), and incorporate the patient packet labeling into the final product packaging configuration.
QOS for Section 3.2.P.2 is not updated since the changes listed above have no impact.

3.2.P.3 Updated QOS and Section 3.2.P.3 in the main body of the current module. Added Abbott Ireland Vascular Division, Mervue Business Park, Galway, Ireland as a subassembly manufacturer in Sections 3.2.P.3.1, 3.2.P.3.3 and 3.2.P.3.5.
Updated Section 3.2.P.3.3 Description of Manufacturing Process Controls to include a patient packet in final assembly.

3.2.P.5 Updated QOS and Section 3.2.P.5 in the main body of the submission. Section 3.2.P.5.3, Validation of Analytical Procedures, is updated with reproducibility data from the method transfer to Clonmel, Ireland site for RTM2037097 (Identity, Content Uniformity, and Total Content), RTM2050930 (Drug Release) and RTM2049690 (Degradation Products).
Added new batch description and batch analyses data for 35 additional SPIRIT IV clinical lots and four developmental stability lots in Section 3.2.P.5.4.
Updated the following Justifications of Specifications (Section 3.2.P.5.6):

- Particulate Matter (Beaker and Tracking): added additional beaker data from SPIRIT IV clinical lots. Added stability and device aging data from

tracking method.
- BHT: added stability data.

3.2.P.7 Updated QOS and Section 3.2.P.7 in the main body of the current module. Updated the packaging validation study results section with data for the 6-month time point under real time storage conditions. Removed references to the paper IFU (as a result of the implementation of eIFU), and included information on the patient packet, which has been incorporated into the final product packaging configuration. Packaging validations include the patient packet.

3.2.P.8 Updated QOS and Section 3.2.P.8 in the main body of the current module. Updated formal stability tables with up to 6-month data; updated site-specific stability tables with up to 3-month data, updated clinical stability tables with up to 12-month data and included supporting stability tables with up to 20-month data. Stress studies are completed and data are presented as well. The postapproval commitment is updated.

QUALITY OVERALL SUMMARY

Introduction

The XIENCE™ V Rapid Exchange (RX) Everolimus Eluting Coronary Stent System and the XIENCE™ V Over-the-Wire (OTW) Everolimus Eluting Coronary Stent System (EECSS) are drug eluting stent systems developed and manufactured by Abbott Vascular. These products are intravascular coronary stents that contain 100 $\mu g/cm^2$ of the anti-proliferative drug everolimus and remain as a permanent implant in the treated patient. The XIENCE™ V EECSS is intended for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length $\leq$ 28 mm) with reference vessel diameter of 2.5 mm to 4.25 mm.

3.2.S Drug Substance

3.2.S.7 Stability

Container Configuration I

The container closure and filling procedure are comparable to that used by Novartis and described in NDA 21-560 and NDA 21-628 with the exception of the size of the bag and the amount of drug substance in the bag. The data from Novartis' NDAs are directly applicable to the Configuration I container closure system. The drug substance will be stored frozen at a temperature of -20°C for up to 48 months which is the same storage conditions proposed by Novartis in their IND (52,003). For everolimus stored in Configuration I packaging, Abbott Vascular does not intend to perform post approval stability studies. Those stability studies will be performed by Novartis in support of their IND/NDAs.

Container Configuration II

The primary stability study (E-80) has been initiated on two vendor lots of the drug substance stored at -20°C. The drug substance stability lots for Study E-80 were lots manufactured by Novartis using the commercial process, site, and scale. Data have been collected for up to nine months from one lot and six months from the second lot. The primary stability study includes: a long-term evaluation at -20°C conducted in compliance with ICH Q1A(R2), Stability Testing of New Drug Substances and Products; an excursion sub-study conducted from -20°C to 20 – 25°C; and a photostability arm per ICH guideline Q1B, Stability Testing: Photostability Testing of New Drug Substances and Products. The study results met the protocol acceptance criteria for long-term evaluation, excursion, and photostability. No trends were detected in any of the key parameters tested.

In addition, supplemental stability data were generated with one lot of everolimus stored at -30°C in an amber glass bottle in double polyethylene bags for the first three months, then subsequently stored at -30°C in Configuration II, for additional 12 months. A stress study was conducted on one vendor lot of the drug substance. The material was stored per the ICH guideline Q1B. Testing methods used for all stability samples are comparable to the analytical procedures described in Novartis' NDA 21-560 and NDA 21-628. The stability data show that the drug substance is stable in Container Configuration II at -30°C for fifteen months and at -20°C for up to nine months.

A proposed storage condition of -20°C and a retest dating period of 12 months for everolimus drug substance stored in Container Closure Configuration II will be based on the real time data for the primary stability studies in Configuration II packaging. Postapproval, Abbott Vascular proposes to test one additional lot per year in addition to the (primary) Stability Study E-80. Reference 3.2.S.7 for a summary of the primary stability and secondary stability results.

3.2.P Drug Product

3.2.P.3 Manufacture

Production of the XIENCE™ V EECSS requires use of multiple facilities for manufacturing, sterilization, testing, storage and related processes. All of these facilities and processes are governed by applicable sections of 21 CFR Part 820 and Parts 210/211. A list of the manufactures of the drug product is provided in Table 5.3-1 below.

Table 5.3-1 List of XIENCE™ V Manufacturers and Service Providers

Name and Address	Operations Performed
Abbott Vascular 26531 Ynez Rd. Temecula, CA 92591	Manufacturing
Abbott Vascular 43201 Zevo Road Temecula, CA 92591	Manufacturing
Abbott Vascular Cashel Rd. Clonmel, Tipperary, Ireland	Manufacturing
Abbott Ireland Vascular Division Mervue Business Park, Galway, Ireland	Manufacturing
Sterigenics LA 4900 S. Gifford Avenue Los Angeles, CA 90058	Sterilization Related
Sterigenics UK Cotes Park Industrial Est. Somercotes, United Kingdom DE55 4NJ	Sterilization Related
Nelson Labs 6280 South Redwood Rd Salt Lake City, UT 84123	Sterilization Related
SteriPro Labs 687 S. Wanamaker Ave. Ontario, CA 91761	Sterilization Related
SteriPro Labs 1500 W. Thorndale Ave. Itasca, IL 60143	Sterilization Related
ACTA Labs 27082 Burbank St. Foothill Ranch, CA 92610	Testing

Table 5.3-1 List of XIENCE™ V Manufacturers and Service Providers (cont'd)

Name and Address	Operations Performed
West Coast Analytical 9240 Santa Fe Springs, Rd Santa Fe Springs, CA 90670	Testing
Spectral Data Services Inc. 818 Pioneer Champaign, IL 61820	Testing
Microchem Laboratories Cloghcranc, Dungarvan, Waterford, Ireland	Testing
NAMSA 9 Morgan Irvine, CA 92618	Testing
Irvine Analytical Labs 10 Vanderbilt Irvine, CA 92618	Testing

The delivery system subassemblies, which make up the rapid exchange (RX) or the over-the-wire (OTW) platforms, are manufactured using the same inherent technologies and equipment as those currently used to produce the MULTI-LINK VISION™ and MULTI-LINK MINI VISION™ Coronary Stent Systems.

The stent implant is the same as that which is currently marketed in the United States for the [bare metal] MULTI-LINK VISION™ stent and MULTI-LINK MINI VISION™ stent P020047/S007).

The stent surface is prepared for coating, and then a PBMA primer layer and the PVDF-HFP drug matrix layer are applied to the stent via a spray-coating process. The drug coated stent is placed onto a stent delivery system to create a Finished Goods (FG) device and then placed into the primary (pre-sterile) packaging. The labeled, packaged product is shipped to a vendor for EtO sterilization and, upon return from the sterilizer, is further packaged into a secondary (post-sterile) foil pouch, purged of air and filled with inert gas. The figure below shows a schematic of the XIENCE™ V manufacturing process.

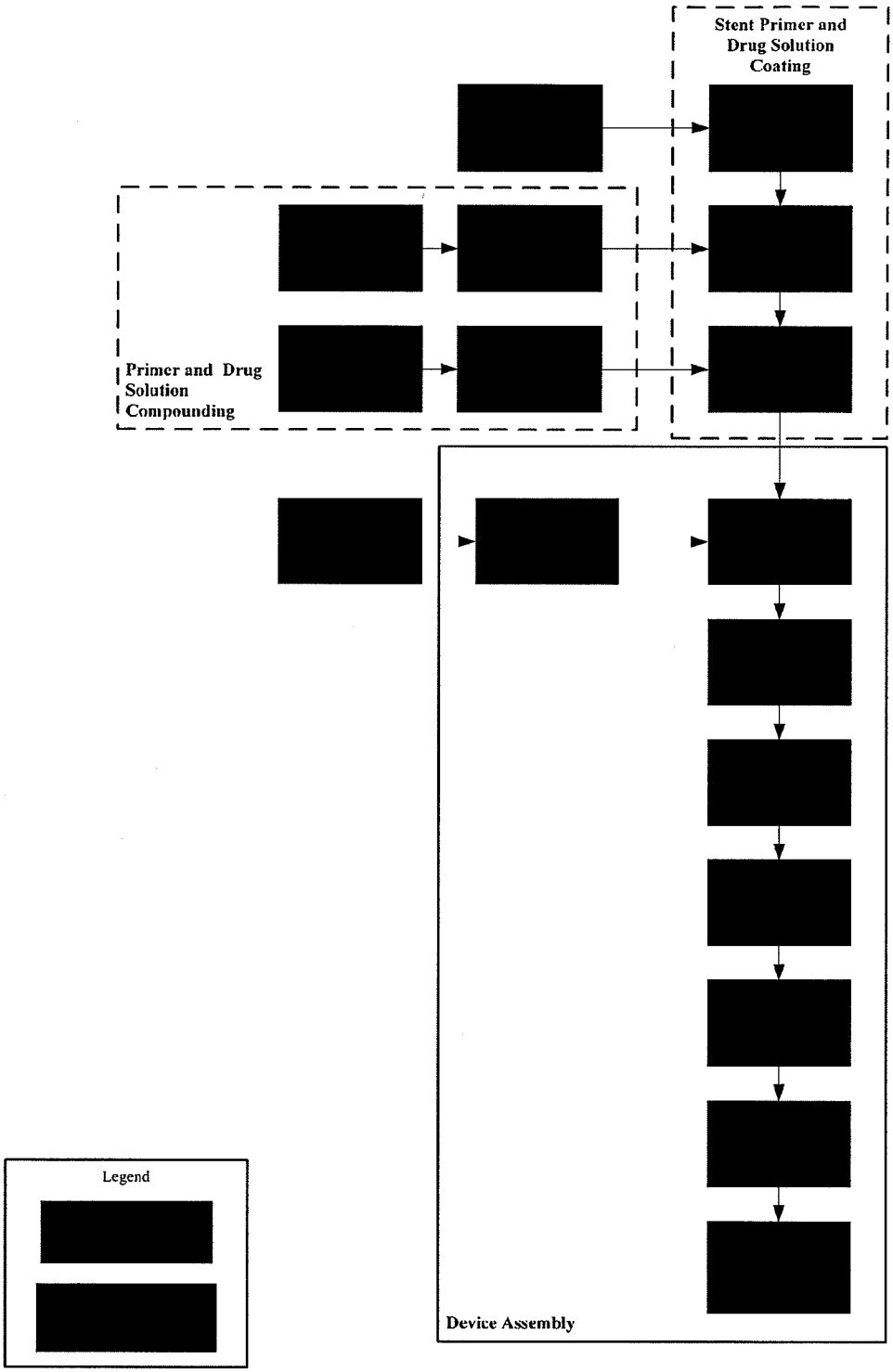


Figure 5.3-1 Manufacturing Overview

SECTION 5.0
XIENCE V EVEROLIMUS ELUTING CORONARY STENT SYSTEM DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) is a combination product comprised of a device (stent system) and a drug coating (everolimus in a polymer coating). The XIENCE V EECSS was designed to meet several key performance objectives. The FDA approved and proven MUTLI-LINK VISION® and MULTI-LINK MINI VISION® Coronary Stent Systems were chosen because these systems offered a flexible stent with thin struts and excellent deliverability. A thin, biocompatibility drug coating was also very important. The drug coating components were chosen because these materials were efficacious with reduced drug loading, stable polymers, offered robust coating integrity, and were shown to be both hemocompatible and compatible with coronary vasculature.

The XIENCE V RX EECSS consists of the coated L-605 Cobalt Chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on a MULTI-LINK RX VISION or MULTI-LINK MINI VISION RX delivery system, respectively. Similarly, the XIENCE V OTW EECSS consists of the coated MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on a MULTI-LINK OTW VISION or MULTI-LINK MINI VISION OTW delivery system, respectively.

5.1 Stent

The XIENCE V Everolimus Eluting Coronary Stent (EECS) is a balloon expandable stent fabricated from a single piece of medical grade L-605 Cobalt Chromium (CoCr) alloy. This alloy can be formed into thinner stent struts than traditional stainless steel stents, and provides a more flexible, low delivery system profile while maintaining adequate radiopacity and strength.

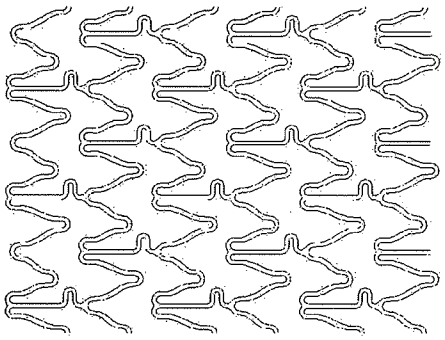
Design

There are two stent designs for the XIENCE V EECS: small and medium. The small XIENCE V stent design (2.5, 2.75, and 3.0 mm diameters) is identical to the MULTI-LINK MINI VISION stent for the 2.5 diameter, and the MULTI-LINK VISION stent for the 2.75 mm and 3.0 mm diameter. The medium XIENCE V stent design is identical to the medium MULTI-LINK VISION stent for the 3.5 mm and 4.0 mm diameters. All stent diameters will be available in 8-28 mm lengths as shown in Table 5-1.

Table 5-1 The XIENCE V Stent Sizes

Stent Design	Predicate Platform	Stent Diameter (mm)	Stent Lengths (mm)
Small	MINI VISION	2.5	8, 12, 15, 18, 23, 28
	VISION	2.75	8, 12, 15, 18, 23, 28
	VISION	3.0	8, 12, 15, 18, 23, 28
Medium	VISION	3.5	8, 12, 15, 18, 23, 28
	VISION	4.0	8, 12, 15, 18, 23, 28

Figure 5-1 includes the stent expansion diameters, stent free area and several stent design features for both the small and medium XIENCE V stents. Figure 5-2 shows digital photographs of the small XIENCE V stent in its crimped and expanded state. Similarly, Figure 5-3 shows photographs of the medium XIENCE V stent in its crimped and expanded state.

Small XIENCE V Stent	
	
Expansion	Balloon expandable
Material	L-605 Cobalt-Chromium (CoCr) alloy
Expansion Diameters (mm)	2.5, 2.75, and 3.0 (post-dilated to 3.5)
Lengths (mm)	8, 12, 15, 18, 23, and 28
Number of Crests per Ring	6
Number of Links per Ring	3
Strut Thickness (inch)	0.0032

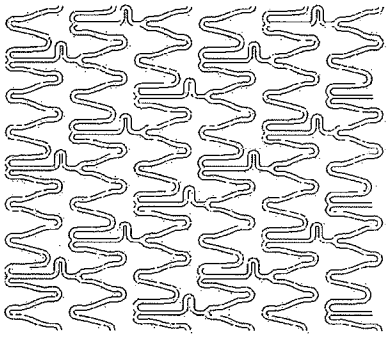
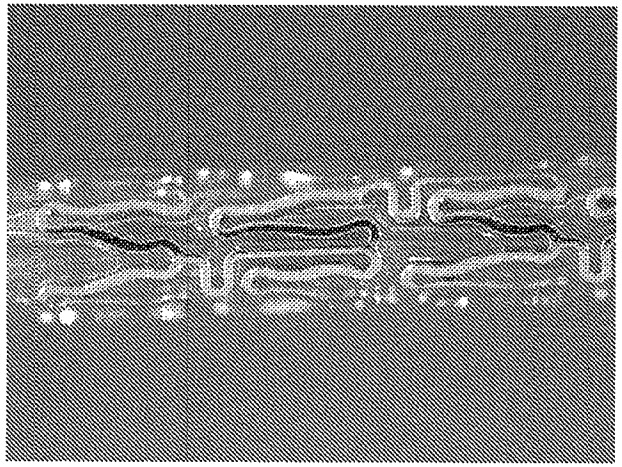
Medium XIENCE V Stent	
	
Expansion	Balloon expandable
Material	L-605 Cobalt-Chromium (CoCr) alloy
Expansion Diameters (mm)	3.5 and 4.0 (post-dilated to 4.5)
Lengths (mm)	8, 12, 15, 18, 23, and 28
Number of Crests per Ring	9
Number of Links per Ring	3
Strut Thickness (inch)	0.0032

Figure 5-1 Description of the XIENCE V EECSS Stent Designs: The length, strut thickness, and number of links per ring are identical across designs while the expansion diameter and number of crests per ring varies.

A.



B.

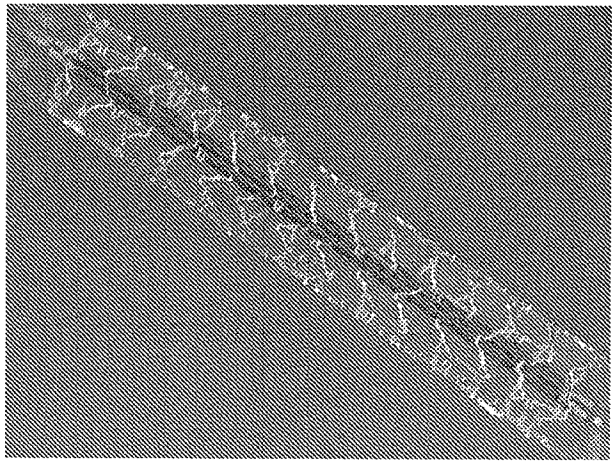
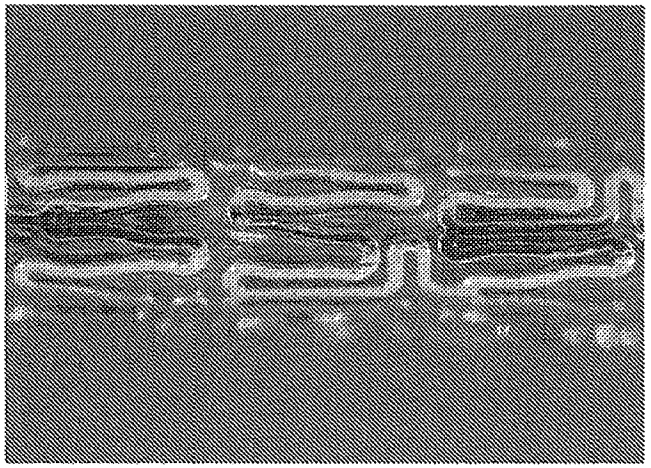


Figure 5-2 Small XIENCE V Stent - Digital photographs showing the small XIENCE V stent in A) crimped and B) expanded forms

A.



B.

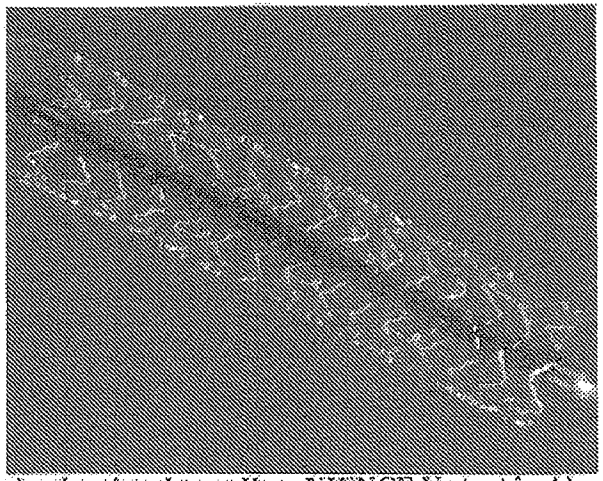


Figure 5-3 Medium XIENCE V Stent Design - Digital photographs showing the medium XIENCE V stent in A) crimped and B) expanded forms.

Material
The XIENCE V EECS is comprised of medical grade L-605 cobalt chromium (CoCr) alloy tubing conforming to ASTM Standard F90. A majority of the ASTM standards and test methods for L-605 CoCr alloy tubing generally refer to bar, wire, sheet, and strip testing. Abbott Vascular has adopted the relevant sections of these standards to ensure compliance with ASTM Standard F90.

5.2 Delivery System Platforms

The XIENCE V EECSS delivery system will be available in two platforms: the XIENCE V RX EECSS (Rapid Exchange (RX)) and the XIENCE V OTW EECSS (Over-the-Wire (OTW)). The balloon portions of these delivery systems are identical, the distal portions of these systems are identical in design and materials, and the proximal ends are specifically designed to accommodate either the RX or OTW platform. Figure 5-4 is a diagram of XIENCE V RX and OTW EECSS components.

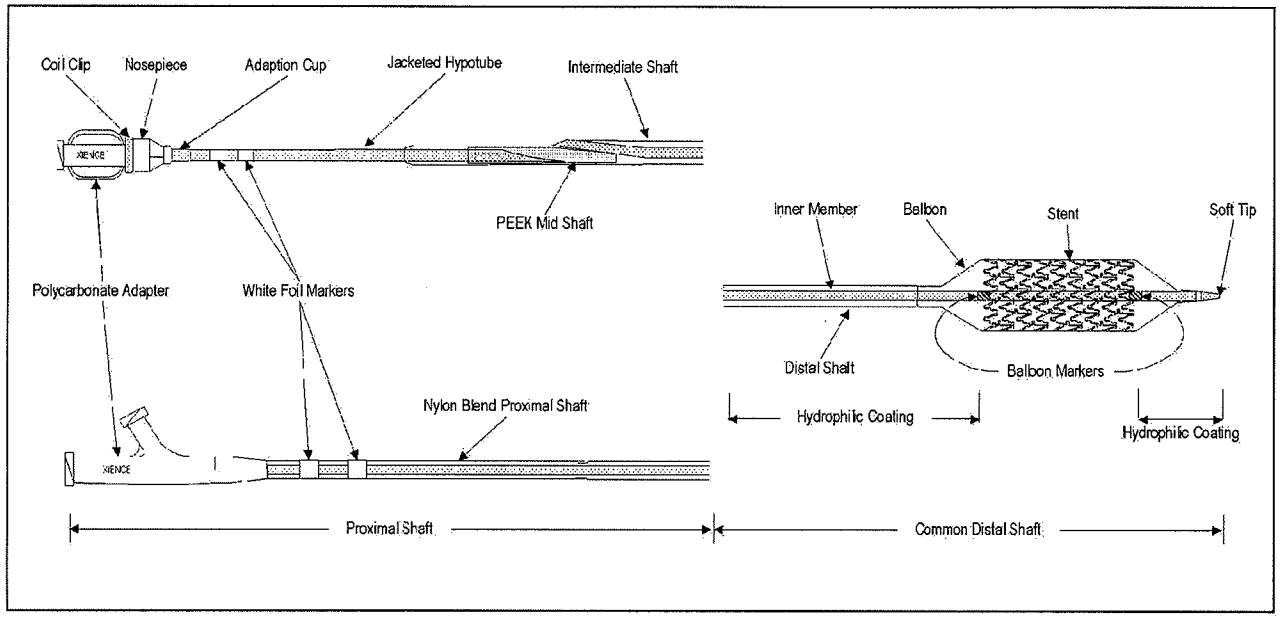


Figure 5-4 Similarities and Differences in Design between the XIENCE V RX and XIENCE V OTW EECSS. A diagram detailing A) XIENCE V RX and B) XIENCE V OTW Everolimus Eluting Coronary Stent System (EECSS). The proximal shaft comprises the unique features of these systems while the distal shaft is identical.

5.2.1 The Rapid Exchange (RX) Delivery System

The XIENCE V RX EECSS is similar in design and performance specifications to the MULTI-LINK RX VISION CSS and the MULTI-LINK MINI VISION RX CSS.

Design

Like other Abbott Vascular RX coronary stent systems and coronary dilatation catheters, the XIENCE V RX EECSS combines a single lumen proximal shaft with a dual lumen mid-shaft and a co-axial lumen distal shaft to create the rapid exchange capability. The single lumen proximal shaft connects the intermediate/distal shaft with the inflation port of the catheter. The guide wire exit notch is located at the proximal end of the junction between the intermediate shaft and the mid-shaft support. The overall length of the catheter is 143 cm. Figure 5-5 illustrates the components and dimensions.

A single arm adapter is attached to the proximal end of the catheter and accesses the inflation/deflation lumen. The proximal shaft is thermally bonded to an adaptation cup that is mechanically sealed to the single arm adapter with a nosepiece, which is threaded to then bonded on the single arm adapter.

There are two non-radiopaque markers on the proximal shaft of the XIENCE V RX EECSS. The two markers, located 95 cm and 105 cm proximal to the distal tip, indicate when the distal tip of the catheter exits the tip of a brachial or femoral guiding catheter, respectively.

A 0.014-inch or smaller diameter guide wire can be used in the guide wire lumen. The guide wire exits the guide wire lumen at the guide wire exit notch, which is formed at the junction of the mid-shaft and the intermediate shafts. Proximal to this point, the guide wire runs externally alongside the proximal shaft of the catheter.

Two radiopaque balloon markers located on the distal segment of the inner member are positioned to mark the working length of the balloon. The stent is mounted such that the markers reflect the expanded stent length. The radiopaque markers fluoroscopically aid in positioning the stent and the delivery system for post-deployment dilation during the procedure.

Table 5-2 includes the product labeling specifications for the XIENCE V RX EECSS. A detailed protocol for XIENCE V RX EECSS preparation will be included in the "Instructions for Use" (IFU) provided with the product.

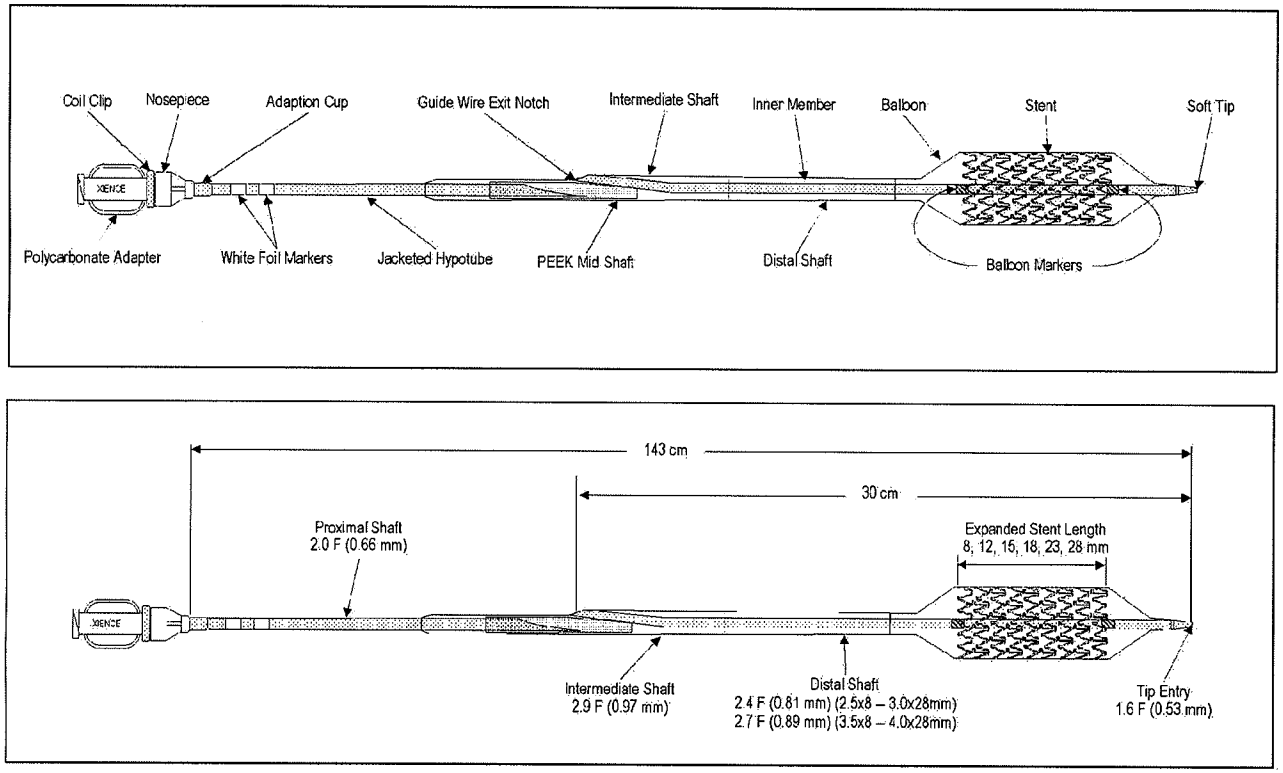


Figure 5-5 The XIENCE V RX EECSS Components and Dimensions (Not to Scale). All dimensions are nominal.

Table 5-2 Device Specifications for the XIENCE V RX EECSS

Model Number	Stent Diameter (mm)	Stent Length (mm)	Crimped Stent Profile (in)	Rated Burst Pressure (atm)	System Working Length (cm)
1009539-08	2.5	8	0.043"	16	143
1009539-12	2.5	12	0.043"	16	143
1009539-15	2.5	15	0.043"	16	143
1009539-18	2.5	18	0.043"	16	143
1009539-23	2.5	23	0.043"	16	143
1009539-28	2.5	28	0.043"	16	143
1009540-08	2.75	8	0.043"	16	143
1009540-12	2.75	12	0.043"	16	143
1009540-15	2.75	15	0.043"	16	143
1009540-18	2.75	18	0.043"	16	143
1009540-23	2.75	23	0.043"	16	143
1009540-28	2.75	28	0.043"	16	143
1009541-08	3.0	8	0.043"	16	143
1009541-12	3.0	12	0.043"	16	143
1009541-15	3.0	15	0.043"	16	143
1009541-18	3.0	18	0.043"	16	143
1009541-23	3.0	23	0.043"	16	143
1009541-28	3.0	28	0.043"	16	143
1009542-08	3.5	8	0.048"	16	143
1009542-12	3.5	12	0.048"	16	143
1009542-15	3.5	15	0.048"	16	143
1009542-18	3.5	18	0.048"	16	143
1009542-23	3.5	23	0.048"	16	143
1009542-28	3.5	28	0.048"	16	143
1009543-08	4.0	8	0.050"	16	143
1009543-12	4.0	12	0.050"	16	143
1009543-15	4.0	15	0.050"	16	143
1009543-18	4.0	18	0.050"	16	143
1009543-23	4.0	23	0.050"	16	143
1009543-28	4.0	28	0.050"	16	143

Note: All dimensions are nominal.

5.2.2 The Over-the-Wire (OTW) Delivery System

The XIENCE V OTW EECSS is similar in design and performance specifications to the MULTI-LINK OTW VISION CSS and the MULTI-LINK MINI VISION OTW CSS.

Design

Like other Abbott Vascular OTW coronary stent systems and coronary dilatation catheters, the XIENCE V OTW EECSS is comprised of a coaxially designed shaft with a balloon near the distal tip. The coaxial shaft consists of a tubular inner and outer member. The annular space between the inner and outer members provides a lumen for inflating and deflating the balloon; it is accessed through the side arm of the proximal adapter. The inner member of the system permits the use of a guide wire. The overall length of the catheter is 143 cm (Figure 5-6).

A sidearm adapter is attached to the proximal end of the catheter to access the inflation/deflation lumen and guide wire lumen. A strain relief provides a transition from the adapter to the shaft.

There are two non-radiopaque markers on the proximal shaft of the XIENCE V OTW EECSS located 95 cm and 105 cm proximal to the distal tip. These markers indicate when the distal tip of the catheter exits the tip of a brachial or femoral guiding catheter, respectively.

A 0.014-inch or smaller diameter guide wire can be used in the guide wire lumen. The guide wire lumen extends from the distal tip to the center port of the sidearm adapter.

Two radiopaque balloon markers are positioned on the distal segment of the inner member to mark the working length of the balloon. The stent is mounted in a manner permitting the markers to reflect the expanded stent length during fluoroscopic positioning of the stent as well as in situating the delivery system for post-deployment dilatation.

Table 5-3 includes the product labeling specifications for the XIENCE V OTW EECSS. A detailed protocol for XIENCE V OTW EECSS preparation will be included in the "Instructions for Use" (IFU) which will be provided with the product.

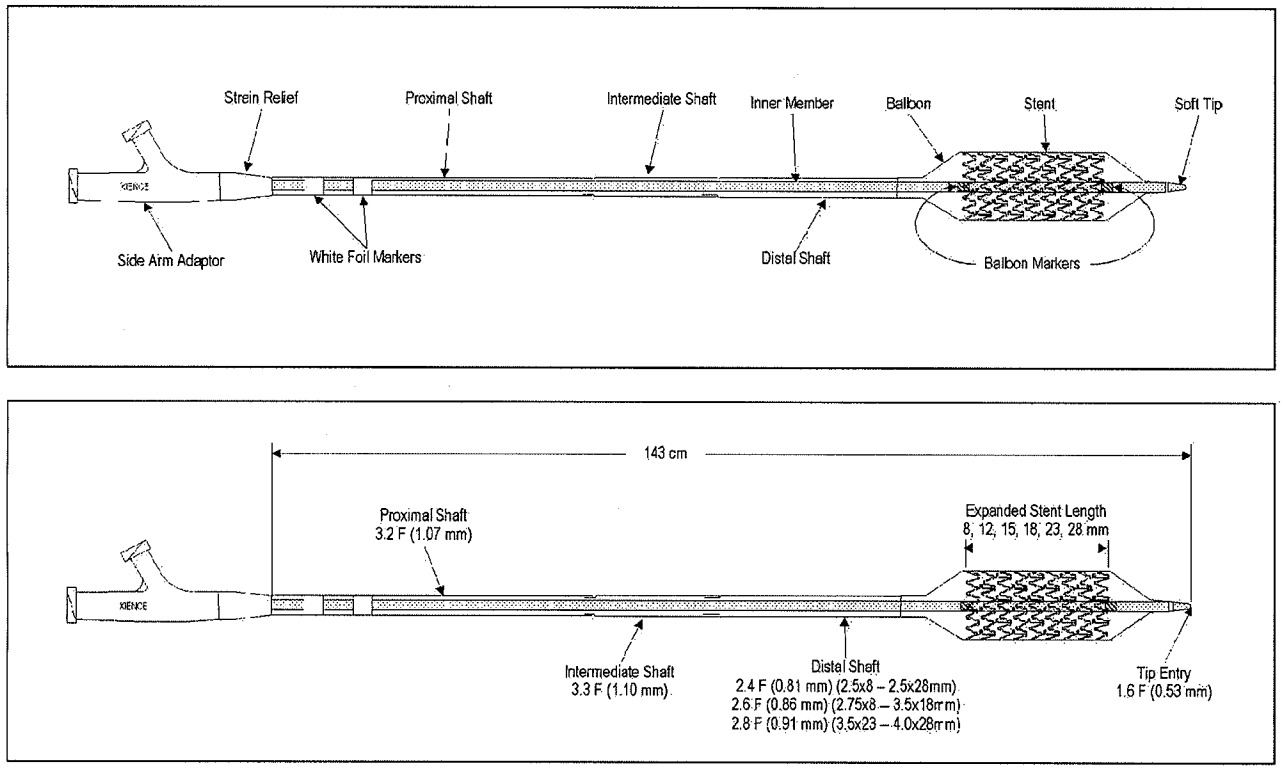


Figure 5-6 The XIENCE V OTW EECSS Components and Dimensions (Not to Scale). All dimensions are nominal.

Table 5-3 Device Specifications for the XIENCE V OTW EECSS

Model Number	Stent Diameter (mm)	Stent Length (mm)	Crimped Stent Profile (in)	Rated Burst Pressure (atm)	System Working Length (cm)
1009545-08	2.5	8	0.043"	16	143
1009545-12	2.5	12	0.043"	16	143
1009545-15	2.5	15	0.043"	16	143
1009545-18	2.5	18	0.043"	16	143
1009545-23	2.5	23	0.043"	16	143
1009545-28	2.5	28	0.043"	16	143
1009546-08	2.75	8	0.043"	16	143
1009546-12	2.75	12	0.043"	16	143
1009546-15	2.75	15	0.043"	16	143
1009546-18	2.75	18	0.043"	16	143
1009546-23	2.75	23	0.043"	16	143
1009546-28	2.75	28	0.043"	16	143
1009547-08	3.0	8	0.043"	16	143
1009547-12	3.0	12	0.043"	16	143
1009547-15	3.0	15	0.043"	16	143
1009547-18	3.0	18	0.043"	16	143
1009547-23	3.0	23	0.043"	16	143
1009547-28	3.0	28	0.043"	16	143
1009548-08	3.5	8	0.048"	16	143
1009548-12	3.5	12	0.048"	16	143
1009548-15	3.5	15	0.048"	16	143
1009548-18	3.5	18	0.048"	16	143
1009548-23	3.5	23	0.048"	16	143
1009548-28	3.5	28	0.048"	16	143
1009549-08	4.0	8	0.050"	16	143
1009549-12	4.0	12	0.050"	16	143
1009549-15	4.0	15	0.050"	16	143
1009549-18	4.0	18	0.050"	16	143
1009549-23	4.0	23	0.050"	16	143
1009549-28	4.0	28	0.050"	16	143

Note: All dimensions are nominal.

Materials
The XIENCE V RX EECSS and the MULTI-LINK RX VISION and MINI VISION RX delivery systems are identical in materials except for the addition of the primer and drug matrix polymers and the anti-proliferative drug for the XIENCE V platform. Similarly, the XIENCE V OTW EECSS and the MULTI-LINK OTW VISION and MINI VISION OTW delivery systems are identical in materials except for the addition of the primer and drug matrix polymers and the anti-proliferative drug for the XIENCE V platform. There is a difference in stent sheath material between the XIENCE V and VISION/MINI VISION systems. This sheath material has been evaluated within biocompatibility and engineering studies with no adverse effect.

5.3 Stent Coating

The XIENCE V EECSS has a coating consisting of two layers: a primer layer and a drug matrix layer. The primer layer is composed of an acrylic polymer and has been approved for other blood contacting applications. The drug matrix layer consists of a durable copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP) blended with the anti-proliferative drug everolimus (Certican®, Novartis Pharmaceuticals Corporation) in an 83%/17% (w:w) proportion respectively and applied to the entire surface (ie, luminal and abluminal) of the primer coated stent. PVDF-HFP is also a component of an approved blood contacting product. PVDF-HFP is blended with everolimus, which is under review in the US for the prevention of organ transplant rejection. Certican (everolimus) has obtained market authorization in over 65 countries. No topcoat layer is used. Figure 5-7 contains scanned electron microscopy (SEM) images of the coated XIENCE V stent in both crimped and expanded states.

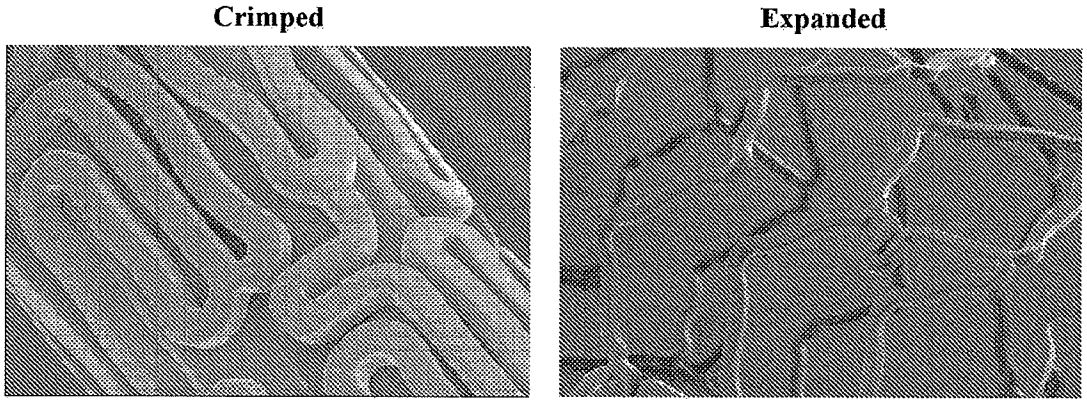


Figure 5-7 Scanned Electron Microscopy (SEM) Images. Images of the coated XIENCE V stent serpentine rings connected by links in both the crimped (60x magnification) and expanded (45x magnification) state.

5.3.1 The Primer Coating

The primer coating is used to improve the adhesion between the L-605 CoCr alloy MULTI-LINK VISION stent and the PVDF-HFP drug matrix. The primer coating [redacted] which renders it resistant to hydrolytic and enzymatic degradation *in vivo*[1].

5.3.2 The Drug Matrix

PVDF-HFP is a random copolymer made from vinylidene fluoride (VDF) and hexafluoropropylene (HFP) monomers. The copolymer is semi-crystalline with glass transition and melting temperatures of [redacted] respectively. The VDF unit in the polymer contains one secondary and one quaternary carbon, while the HFP unit in the polymer is perfluorinated. The high dissociation energy of the C-F bond coupled with the absence of other atoms in the backbone (ie, oxygen, nitrogen, sulfur) renders PVDF-HFP resistant to process-induced degradation, oxidative degradation *in vivo*, and free radical induced degradation *in vivo*. Also, PVDF-HFP contains no reactive functional groups and is stable at physiological conditions (Figure 5-8). Additionally, the elongation strain for the fluoropolymer is approximately [redacted] while the L-605 Cobalt Chromium hypotube can tolerate an elongation strain of 30% its original length. Therefore, coating-related tension failure is not expected to occur. Due to the dissimilarity of the balloon material (Pebax) and PVDF-HFP polymer, the stent coating does not adhere to the balloon material.

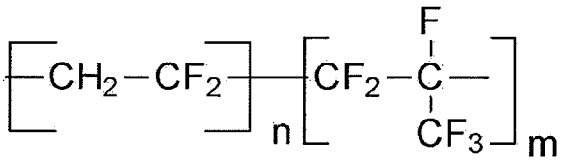


Figure 5-8 Formula for Vinylidene Fluoride and Hexafluoropropylene Copolymer (PVDF-HFP)

PVDF-HFP was chosen as the drug matrix polymer because it met the design objectives for the XIENCE V stent. This material has a history of use in approved coronary applications and proven vascular compatibility, showed excellent mechanical coating integrity, was stable *in vitro* and *in vivo*, showed compatible solubility, coatability and sterilizability, was available in a high purity grade, and demonstrated drug permeability.

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[1] Mark, James E, ed. Physical properties of polymers handbook. Woodbury, N.Y.: American Institute of Physics, 1996, p605-607

[2] Baker, R, Controlled Release of Biologically Active Materials, Wiley-Interscience, 1987, Chapter 3

PVDF-HFP worked well in a simple matrix design, which after evaluating a number of other release systems, was chosen for the XIENCE V system due to the good coating quality and integrity, versatility and reproducibility of the release profile, and ease of manufacturing.

The simple matrix systems consisted of physical blends of drug and PVDF-HFP. Matrix designs are the most manufacturable. A classical matrix system, with solid drug dispersed in a matrix of polymer saturated with drug will release the drug according to a profile that is linear with the square root of time for a significant fraction of its release[3]. Developmental studies showed that by varying the drug to polymer (D:P) ratio and the thickness of the coating, a wide range of release rates could be achieved, and that these release rates were well controlled and reproducible.

The release of the drug from the XIENCE V stent as measured in animal studies is shown in Figure 5-9. This figure shows how the controlled release of everolimus from the XIENCE V stent correlates to the *in vivo* restenosis cascade[4].

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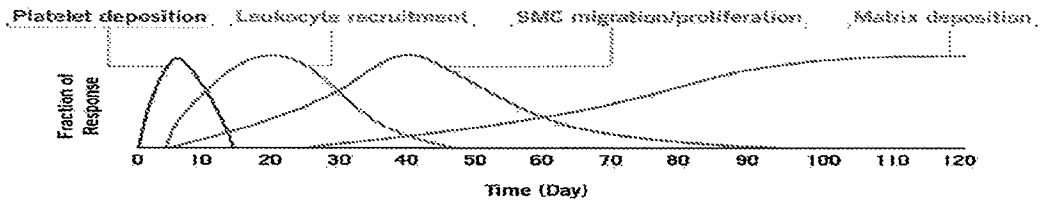
[3] Baker, R,Controlled Release of Biologically Active Materials, Wiley-Interscience, 1987, Chapter

[4] Forrester JS et al. A Paradigm for Restenosis based on Cell Biology: Clues for the Development of New Preventative Therapies. JACC 1991, Vol 17, No 3, 758-69



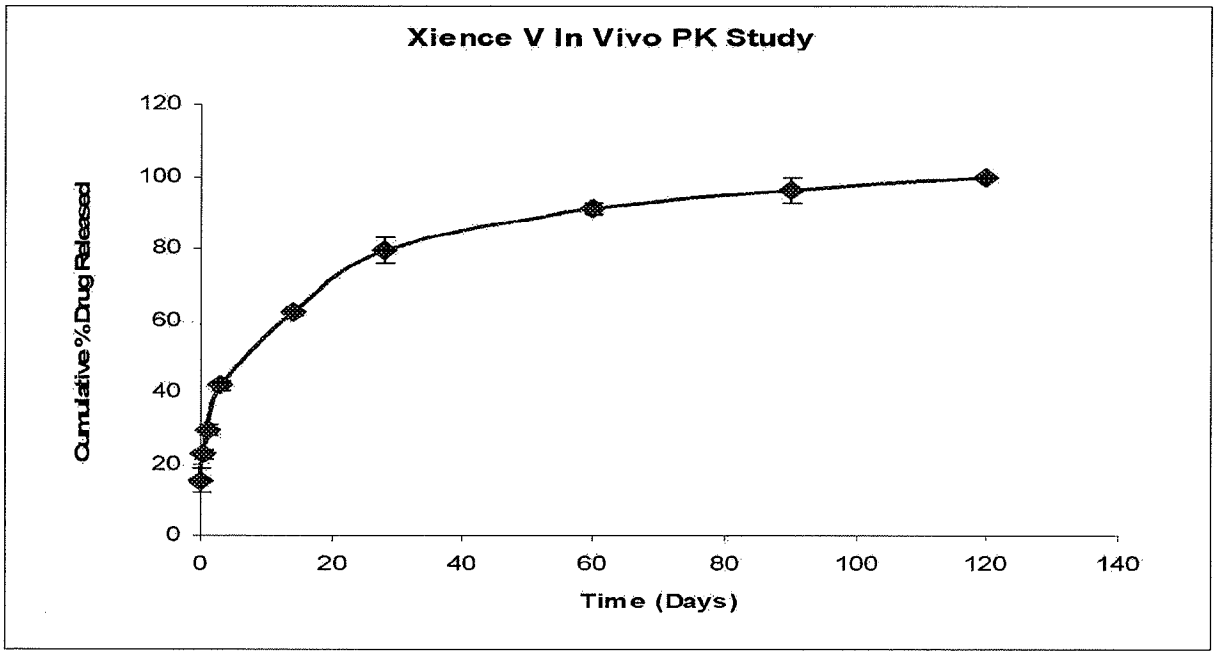


Figure 5-9 Release of Everolimus from the XIENCE V Stent compared to Restenosis Cascade as shown in Animal Pharmacokinetic Studies

5.3.3 The Anti-Proliferative Drug: Everolimus

The active pharmaceutical ingredient in the XIENCE V EECS system is everolimus [40-O-(2-hydroxyethyl)-rapamycin], provided to Abbott Vascular by Novartis Pharmaceuticals Corporation. Everolimus is a novel semi-synthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: sirolimus) is a secondary macrolide metabolite produced by certain actinomycete strains. The structure of everolimus (Figure 5-10) consists of a 2-hydroxyethyl group in position 40 of sirolimus. Sirolimus (Rapamune®; Wyeth) has received global marketing approval for the prophylaxis of renal transplant rejection. In numerous clinical trials, sirolimus used as an adjunctive coating on coronary stents, has been shown to prevent restenosis. A sirolimus-eluting stent has obtained marketing approval in the European Union, Canada, Japan, and the US. Everolimus is a drug that has been evaluated in clinical trials in the US and outside the US for use in conjunction with other medications to prevent heart and renal transplant rejection. Everolimus (Certican) has obtained market approval in over 65 countries.

Additionally, everolimus (Certican) is under review for market approval in the United States and has received two approvable letters from FDA. Novartis continues to work with the FDA towards a final NDA decision using additional clinical data from prospective transplant trials that evaluate a regimen of everolimus with therapeutic drug monitoring and reduced dose Neoral® (cyclosporine, USP) MODIFIED to support the NDA review.

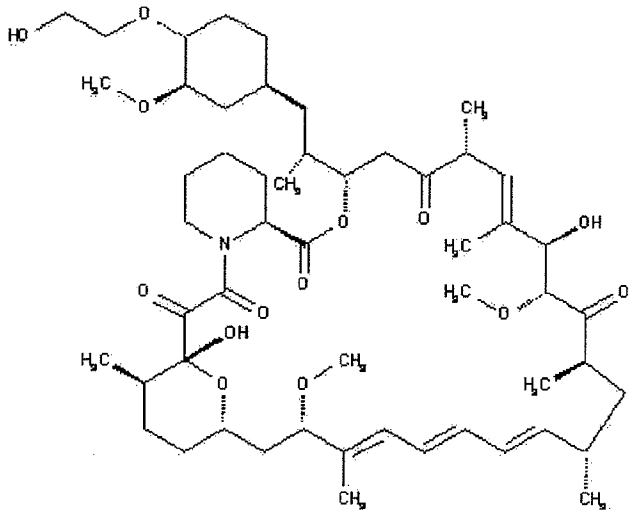


Figure 5-10 Structure of Everolimus

5.3.3.1 Everolimus Mechanism of Action

In comparison with rapamycin, an immunosuppressant of the same class of macrolide compounds, everolimus showed similar systemic exposure and toxicity profiles in pre-clinical studies. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1, two key players in the initiation of protein synthesis, is inhibited. Although not formally proven, it is thought that the everolimus-FKBP-12 complex may bind and interfere with FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin) - a protein that governs cell metabolism, growth and proliferation, and regulates phosphorylation of both p70 S6 kinase and 4E-BP1. This is supported by modeling results using published X-ray structure information which suggest that there is no impediment to the ternary FKBP-12/everolimus/FRAP complex formation.

Everolimus possesses anti-fungal, immunosuppressive and anti-proliferating properties. Under the trade name Certican, everolimus has been studied in preclinical and clinical studies as an anti-rejection therapy used in combination with Neoral (cyclosporine, CsA). Everolimus is an

effective immunosuppressive agent that can act synergistically with CsA for the prophylaxis of acute rejection while concomitantly preventing smooth muscle cell proliferation at the level of the graft vessel.

5.3.3.2 Summary of Novartis' Preclinical Data on Certican

Overview of Preclinical Studies
The potential of everolimus as an immunosuppressant in the indication of solid organ transplantation was demonstrated in rodent and non-human primate models of solid organ allotransplantation using an experimental microemulsion formulation of everolimus for oral application of the compound. Everolimus was well tolerated after single oral administration in acute toxicity studies, and therefore, it has a low potential to affect vital functions following accidental or deliberate overdosing.

In repeated-dose toxicity studies, effects secondary to immunosuppression were evident at higher dosages in all species, and indicate a potential of everolimus to exacerbate infectious background diseases. Major target organs in all animal species were reproductive organs, and males were generally more affected than females. Lesions were most probably related to an endocrine imbalance. This was evidenced in rats by a decrease in plasma testosterone levels as a consequence of an inhibition of key regulators of steroid hormone synthesis. Lungs (increased alveolar macrophages) were identified as rodent-specific target organs, and eyes (lenticular anterior suture line opacities) as rat-specific target organs.

Everolimus was devoid of mutagenic or clastogenic activity, and did not show an oncogenic potential. In reproduction studies, orally administered everolimus was toxic to the conceptus in rats and rabbits. It is therefore recommended that women of childbearing potential should use effective contraceptive measures during the entire treatment period. If women are in early pregnancy when treatment starts, they should be informed about the potential risk to the fetus. In view of the absence of genotoxic effects and the results from male fertility studies, male patients who receive treatment with everolimus should not be prohibited from attempting to father children.

Carcinogenicity Studies
In the mouse and rat 104-week carcinogenicity studies, there was no indication of a tumorigenic potential up to the high dose of 0.9 mg/kg of everolimus, corresponding to an exposure ratio of 8.6 and 0.3, respectively, relative to the maximum recommended dose of 3 mg/day for man.

Reproductive Toxicology Studies
In the 13-week male fertility study in rats, no treatment-related effects were noted at the lowest dose of 0.1 mg/kg. At 0.5 mg/kg, a slight effect on testicular morphology was detected, but there was no difference from

controls in animals after 13 weeks of recovery. There were no adverse effects on reproductive parameters at this dose. At the highest dose of 5.0 mg/kg, males mated, but none of the females became pregnant. Males at 5.0 mg/kg showed marked histopathological changes in the testes (atrophy with germ cell depletion) and epididymides (oligospermia to aspermia). Sperm motility and testicular sperm head count were diminished. Plasma testosterone levels were significantly reduced. After a 13-week recovery period, reversibility of the histopathological changes was complete in only half of the animals, and pregnancy was confirmed in 13/18 inseminated females mated with the treated males. There was no evidence of adverse effects by treating males with everolimus on embryo-fetal parameters.

Female fertility was not affected, but everolimus crossed the placenta, and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity that was manifested as mortality and reduced fetal weight. Increased incidence of skeletal retardation, fetuses with 14 ribs and spontaneous malformations was reported. In rabbits, embryotoxicity was evidenced by an increase in late resorptions.

Effects of everolimus on the pre- and post-natal development of rats did not indicate a specific toxic potential.

Mutagenicity Studies
Everolimus was tested for genotoxic activity in a variety of *in vitro* and *in vivo* tests, covering all relevant endpoints. There was no evidence of a mutagenic or clastogenic activity. Everolimus exposure in the mouse at the doses used in the micronucleus assay was well in excess of that expected at therapeutic doses in humans.

Special and Combination Toxicity Studies
Everolimus did not show a potential to cause contact hypersensitivity on the skin of guinea pigs in the maximization test. Everolimus was not irritating to the skin of rabbits.

The administration of everolimus in combination with CsA to rats and monkeys resulted in changes related to the pharmacological activity of the compounds, and in findings reflecting toxicity, both notably exacerbated when compared to those observed with each of the compounds alone. There were no new target organs in the rat.

Monkeys treated with combinations of everolimus and CsA showed unexpected findings of hemorrhage and arteritis in several organs (gastrointestinal tract [GI] tract, heart, liver, kidneys, lymph nodes and pancreas). In view of the complexity of the possible involved mechanisms, the pathogenesis of arteritis remains uncertain, although the high degree of immunosuppression in connection with a disturbed integrity of the gut could suggest an infectious/inflammatory origin. The low-dose

combination of CsA/everolimus at 50/0.25 mg/kg resulted in a higher degree of immunosuppression than with the compounds alone, but was not associated with arteritis or poor health status as observed with the high-dose combinations.

The combination of everolimus and tacrolimus in rats induced an increased severity of adverse effects and of changes related to immunosuppression when compared with those of either compound alone. The increase in toxicity was particularly pronounced in the cardiovascular and reproductive systems. With the low-dose combination of everolimus and tacrolimus, both at 0.75 mg/kg, there was, however, only slight increases in severity compared with each compound alone. The combination had no relevant effect on the toxicokinetic profile of tacrolimus, whereas exposure with everolimus was markedly increased.

Absorption and Bioavailability

A significant proportion of the absorbed everolimus in the rat, especially at low oral doses, was affected by intestinal first-pass metabolism[5]. The absolute bioavailability of everolimus was 5% in the mouse, 14%-26% in the rat and 6% in the monkey. Studies in Caco-2 cells showed that everolimus was a substrate for the efflux transporter P-gp at low concentrations, but that this efflux was saturated at higher concentrations[6]. The absolute bioavailability of everolimus could not be assessed in man due to the difficulties in providing an appropriate formulation for intravenous administration, and since no non-toxic effect level was identified in the intravenous monkey studies.

Distribution

The *in vitro* distribution of everolimus between blood cells and plasma was concentration dependent over the range of 5 to 5000 ng/mL in the rat, monkey and human, and concentration independent in the mouse.

Everolimus was highly bound to plasma proteins of the mouse (99.9%), and moderately bound in the rat (92%), monkey (84%) and human (75%). The moderate affinity of everolimus for human plasma proteins indicates that a potential drug-drug interaction on the basis of drug protein binding is very unlikely. The extent of protein binding was similar between healthy humans and patients with moderate hepatic impairment.

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[5] Crowe A, Bruelisauer A, Duerr L, et al (1999) Absorption and intestinal metabolism of SDZ-RAD and rapamycin in rats. Drug Metab Dispos; 27(5):627-632.

[6] Crowe A, Lemaire M (1998) *In vitro* and *in vivo* absorption of SDZ RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: Comparison with rapamycin. Pharm Res; 15:1666-1672.

Metabolism
The metabolism of everolimus was investigated in the mouse, rat and monkey after single oral and intravenous doses. In humans, the metabolism of everolimus was investigated in stable renal transplant patients on Neoral after a single oral dose of 3 mg [^{14}C]everolimus.

In all species, generally, the parent drug was the major circulating component in blood, averaging 31%-63% of the total $AUC_{(0\text{-}24\ h)}$ radioactivity in mice, rats and humans and 12% in the monkey. In human blood, 5 major metabolite peaks were present covering, together with unchanged drug, > 80% of the total ^{14}C-AUC. These 5 main metabolites detected in human blood were also present in the blood of the mouse, rat and monkey.

Excretion/Elimination
Excretion of everolimus and its metabolites was predominantly via feces in all investigated species, including man, and was characterized by metabolic clearance. Virtually no parent drug was recovered in the urine and feces. The balance of excretion was almost complete within several days.

Drug-Drug Interaction Potential
The potential for metabolic drug-drug interactions was investigated *in vitro* in human liver microsomes, and in microsomes from recombinant CHO cells expressing individual cytochrome P450 isoenzymes. CYP3A4 was the major P450 enzyme involved in the microsomal biotransformation of everolimus (Km 2-3 µmol/L; V_{max} 46-100 nmol/h/mg microsomal protein)[7].

Everolimus was a competitive inhibitor of the CYP3A substrate CsA (K_i = 2.3 µmol/L), and was also a mixed inhibitor of the CYP2D6 substrate dextromethorphan (K_i = 1.7 µmol/L). The maximum plasma concentration following a daily recommended highest oral dose of 1.5 mg bid of everolimus in human (C_{max}ss: 20.3 ± 8.0 ng/mL) was, however, more than 75-fold below these K_i-values. Therefore, everolimus is unlikely to significantly affect the metabolism of other compounds predominantly cleared by these enzymes.

Prevention of Vascular Proliferation
Everolimus inhibited *in vitro* fetal calf serum-stimulated bovine aortic smooth muscle cell (SMC) proliferation. Oral administration of everolimus (1.0 mg/kg/day, beginning 3 days before vessel injury) to pigs inhibited PTCA-induced intimal thickening by 54% and neointimal area by

[7] Kuhn B, Jacobsen W, Christians U, et al (2001) Metabolism of sirolimus and its derivative everolimus by cytochrome P450 3A4: Insights from docking, molecular dynamics and quantum chemical calculations. J Med Chem; 44:2027-2034.

34%. Additionally, everolimus was efficacious in a rabbit stent model. Rabbits were treated with 2 different oral dosing regimens of everolimus in combination with arterial stenting. The high dose regimen consisted of 1.5 mg/kg/day beginning 3 days prior to stenting and continuing for 14 days following stenting, after which the dose was reduced to 1.0 mg/kg/day for the remainder of the study. The low dose regimen consisted of 1.5 mg/kg/day the day before surgery, which was then reduced to 0.75 mg/kg/day for the remainder of the study. At 28 days post stenting both groups showed 84% endothelialization of the stent. Both treatment regimens significantly reduced neointimal thickness (by 49% for the high dose and 40% for the low dose) and neointimal area (by 32% for the high dose and 24% for the low dose).

These data supported the further investigation of everolimus as a potential therapeutic agent for the reduction of restenosis following PTCA and stenting. In order to avoid the potential side effects and large doses associated with oral administration of everolimus, Abbott Vascular has studied the safety and potential utility of everolimus eluting stents for the prevention of restenosis.

5.3.3.3 Summary of Novartis' Clinical Data on Certican

The purpose of the following discussion is to summarize the safety and efficacy of systemically administered everolimus. Everolimus has been studied extensively in renal and heart transplantation with additional date in lung and liver transplant patients. Therapeutic doses between 1.5 and 3.0 mg/day have been thoroughly evaluated. The use of everolimus in heart transplant studies showed significantly less thickening of the intima in the coronary arteries of transplanted patients in comparison with the control group. These findings support the safety and efficacy of everolimus at doses that exceed the levels eluted from the XIENCE stent. The following data are from Novartis Investigator's Brochure, Edition 9, dated August 27, 2007.

Everolimus, at therapeutic blood levels greater than 3.0 ng/ml, has been shown to be an effective immunosuppressant that has been developed for use in combination with Neoral® (cyclosporine, USP) MODIFIED for the prophylaxis of acute rejection and the prevention of chronic rejection in patients receiving organ transplants. The following is a summary of clinical trials, demonstrating the safety profile of systemic therapeutic levels of everolimus greater than 3.0 ng/ml. Accordingly, the blood levels of everolimus achieved with oral doses used in clinical trials of organ transplant rejection are approximately ten-fold higher than the total *in vivo* systemic exposure with the implantation of XIENCE.

In humans, everolimus dosed twice daily (bid) with CsA yields steady-state drug exposure by day 4 after initiation of therapy in renal and heart transplant recipients. Thereafter, blood levels of drug remain relatively

constant over time through the first post-transplant year. There are no clinically relevant departures from dose proportionality in exposure. Freedom from acute rejection in both renal and heart transplantation is significantly related to everolimus trough concentrations with a lower therapeutic concentration threshold of 3 ng/mL. There is only a small additional increase in freedom from rejection at everolimus trough levels above 8 ng/mL. Although the incidence of decreased thrombocyte counts (< 75 to 100×10^9/L) increases with increasing exposure, the overall incidence in clinical trials was low, and therefore, a precise upper concentration for the therapeutic range could not be identified based on safety concerns. Clinical experience with trough concentrations above 12 ng/mL or doses above 1.5 mg bid is limited. The therapeutic concentration range is recommended as 3 to 8 ng/mL in both kidney and heart transplantation.

Use of Everolimus in Renal Transplantation

Efficacy Summary

In *de novo* renal transplant patients, both doses of everolimus combined with full-dose Neoral had similar efficacy as compared with mycophenolate mofetil (MMF) for efficacy failure (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) at 6 and 12 months, and were comparable at 36 months. The therapeutic drug monitoring analyses strongly suggest that graft survival would be improved with the use of everolimus concentration monitoring. Patient survival was excellent in all groups.

In studies B251 and B201 in *de novo* renal transplant patients, both doses of everolimus (1.5 and 3 mg/day) administered in combination with Neoral and corticosteroids was equivalent to MMF with respect to efficacy failure at 6 months post-transplantation (ie, biopsy-proven acute rejection, graft loss, death, or loss to follow-up). Equivalence for efficacy failure was maintained at 12 months. For the co-primary endpoint of graft loss, death, or loss to follow-up at 12 months post-transplantation, in study B251 (mostly US centers), everolimus 3 mg was equivalent to MMF, and both 95% and 97.5% confidence intervals (CIs) for everolimus 1.5 mg vs. MMF slightly exceeded the limit of equivalence. In study B201 (mostly European centers), everolimus 1.5 mg was equivalent to MMF, and both 95% and 97.5% CIs for everolimus 3 mg vs. MMF slightly exceeded the limit of equivalence. The incidence of late-occurring biopsy-proven acute rejections (ie, days 451 to 1170) was low in all groups. Between 1 and 1170 days, the incidence of deaths was similar in all groups for studies B251 and B201, respectively: everolimus 1.5 mg - 12 patients (6%) / 15 patients (8%), everolimus 3 mg - 13 patients (7%) / 18 patients (9%), and MMF – 10 patients (5%) / 16 patients (8%).

As the use of everolimus with full-dose Neoral is associated with renal dysfunction in some renal patients, it has been important to recognize that

the efficacy of everolimus is maintained in combination with reduced-dose Neoral. This was initially demonstrated in study B156, a prospective trial using the 3 mg/day dose of everolimus, in which rejection efficacy remained excellent despite reduction of Neoral exposure by about 35%. Amendments to the Phase 3 studies showed that late rejection was very rare when CsA trough levels were reduced to about 75 ng/mL at 18-31 months after transplantation. This study demonstrated excellent efficacy in both the Neoral full- and reduced-dose groups, thus demonstrating that efficacy is maintained when CsA exposure is reduced in combination with everolimus.

The most recent renal studies A2306 (without Simulect) and A2307 (with Simulect induction), which both used TDM prospectively, demonstrated better renal function, at 12 months, than that previously observed in the phase 3 studies, B251, B201 and B156. Everolimus 1.5 and 3 mg in combination with corticosteroids and a reduced Neoral dose regimen was effective in the prevention of graft rejection after renal transplantation at 12 months post-transplant. The incidence of efficacy failure and biopsy-proven acute rejection was low in both studies, and comparable to that observed in the pivotal studies, B251 and B201, and study B156. Long term outcomes at 36 months in the A2306 and A2307 extensions were similar to those at 12 months and no statistically significant differences between groups were observed in efficacy and safety parameters.

Safety Summary

In *de novo* renal transplant patients, both fixed doses of everolimus (1.5 mg and 3 mg) were generally well-tolerated, although there was a tendency towards a higher incidence of nonfatal SAEs and discontinuations of study medication due to AEs with everolimus compared with MMF. Thrombocytopenia was observed more frequently in both everolimus groups compared with the MMF group. Everolimus plus full-dose CsA was associated with dose related increases in mean serum creatinine and decreases in creatinine clearance compared with MMF. Mean testosterone was significantly lower in both everolimus groups compared with the MMF group; however, at 12 months, mean testosterone was within the normal range in all treatment groups. Elevations of serum lipids occurred more frequently in everolimus-treated patients than in the MMF group, with greater changes in the everolimus 3 mg group compared with the 1.5 mg group.

In renal study A2306, with a reduced-dose Neoral regimen and concentration controlled everolimus, mean and median serum creatinine was low, and stable from 2 or 3 months onwards to 12 months. The inclusion of only approximately 50% of the original randomized patients into the extension of this study limits meaningful conclusions made for this extension.

Use of Everolimus in Heart Transplantation

Efficacy Summary

In the heart transplant study B253, both doses of everolimus (1.5 and 3 mg/day) were superior to azathioprine (AZA) for efficacy failure (acute rejection ISHLT ≥ grade 3A, acute rejection associated with hemodynamic compromise, graft loss, death, or loss to follow-up) at 6, 12, 24, and 48 months. This finding was primarily due to a reduction in the incidence of acute rejection (ISHLT ≥ grade 3A) in the everolimus groups. As discussed above for renal transplantation, TDM is expected to enhance the efficacy and safety of everolimus in heart transplantation. There is a clear reduction in the incidence of acute rejection with average everolimus trough levels > 3 ng/mL. A small subset of patients was enrolled up to 72 months prior to study discontinuation. The number of patients was too small to reach any conclusion of their data.

The heart study also demonstrated a significant reduction in average maximum intimal thickness of the coronary arteries from baseline at 12 and 24 months for both doses of everolimus compared with the AZA group. Thus, both doses of everolimus were superior with respect to the incidence of allograft vasculopathy at 1 year post-transplantation, and the 1.5 mg group was also superior at 24 months.

Everolimus, at fixed doses of 1.5 and 3 mg/day, administered in combination with Neoral and corticosteroids to primary heart allograft recipients was superior to a standard treatment with 1-3 mg/kg/day of AZA with regard to the incidence of efficacy failure at 6, 12, 24, and 48 months and everolimus 3 mg/day was superior to 1.5 mg/day. In particular, significantly fewer acute rejection episodes were reported in both everolimus dose groups, and this effect was dose related. Twelve, 24-, and 48-month patient and graft survival was excellent in all groups, with no significant differences between everolimus and AZA. Specifically, in the long-term, open-label extension period (48 months) between Days 1 and 1,530, the incidence of deaths was similar in all treatment groups: everolimus 1.5 mg - 32- patients (15.3%), everolimus 3 mg - 34 patients (16.1%), and AZA - 30 patients (14%).

Safety Summary

In *de novo* heart transplant patients, the incidence of nonfatal SAEs and discontinuations of study medication due to AEs was significantly higher in the 3 mg fixed dose of everolimus compared with the 1.5 mg fixed dose of everolimus and azathrioprint. The overall infection rates were comparable between groups; however, there was a significantly higher incidence of viral infections (particularly CMV infections) in the AZA group than in the everolimus groups. Decreases in mean hemoglobin and platelet counts occurred more frequently in everolimus-treated patients than in the AZA group, and were associated with everolimus dose level. Conversely, leukopenia was more frequent in the AZA group. Mean LDLs

and HDLs were not significantly different between groups. Mean triglycerides were elevated in both everolimus groups compared with the AZA group. Everolimus was associated with dose related increases in mean serum creatinine and decreases in creatinine clearance that were significant compared with the AZA group, but these values were stable from 12 to 24 months. Mean testosterone was significantly lower in both everolimus groups compared with the AZA group.

Use of Everolimus in Lung Transplantation

Efficacy Summary

In maintenance lung transplant patients (study B159), everolimus showed unique efficacy not only to prevent acute rejection, but also slowed the progression in airway dysfunction. The onset of bronchiolitis obliterans syndrome (BOS) in this patient population portends limited long-term survival. Everolimus 3 mg/day was superior to AZA 1-3 mg/kg/day for the primary efficacy endpoint (incidence of FEV_1 decline > 15% of the baseline value from the study entry value, graft loss, death or loss to follow-up during the first 12 months after the initial dose of study medication). The incidence rates for this composite primary endpoint were 22% and 34% for everolimus 3 mg/day and AZA, respectively ($p = 0.0455$). The incidence rate for $FEV_1 > 15\%$ was 16% vs. 28% ($p=0.034$), and for treated acute rejection episodes was 8% vs. 32% ($p < 0.001$), showing a significant advantage of everolimus vs. AZA, while the incidence of deaths (3% vs. 9%, $p = 0.061$) and all other secondary efficacy endpoints demonstrated a trend in favor of everolimus. More AZA patients discontinued study medication due to unsatisfactory therapeutic effects, while more patients discontinued study medication in the everolimus group due to AEs.

The primary efficacy endpoint (ie, incidence of FEV_1 decline >15% of the baseline value from study entry value, graft loss, death or loss to follow-up during the first 12 months after the initial dose of study medication) was 22% and 34% for everolimus 3 mg/day and AZA, respectively, and the difference in favor of everolimus was significant ($p = 0.0455$).

Graft losses and deaths were numerically lower in the everolimus group. Everolimus was superior to AZA with regard to the incidence of FEV_1 decline >15% of the baseline value from study entry value ($p = 0.034$). Everolimus was also superior to AZA with regard to the incidence of BOS and decline in FEV_1 >15% ($p = 0.014$) and the incidence of treated acute rejection episodes ($p < 0.001$). In addition, all other efficacy variables showed a trend in favor of everolimus.

By 24 months, the incidence of acute rejection remained significantly lower in the everolimus patients as compared to AZA. However, the incidence of the primary composite endpoint did not differ between treatment groups (everolimus: 43.6%; AZA: 44.6%) and rates of graft loss

and death were similar. The incidences of $\Delta FEV_1 > 15\%$ (34.7% vs 41.1%) and all other secondary efficacy endpoints were numerically lower in the everolimus group. There was also a trend in favor of everolimus with regard to the mean decline in FEV_1 from study entry to 24 months.

Safety Summary

Everolimus use in lung transplantation (study B159) was associated with its anticipated side effect profile of CsA nephrotoxicity, lipid elevation, clinically silent endocrine abnormalities and an increased risk of infection. The incidence of overall infections (82% vs. 80%), bacterial infections (35% vs. 17%) and fungal infections (28% vs. 14%) were higher in the everolimus group vs. the AZA group. At 12 months the incidence of viral infections (30% vs. 29%), and specifically, CMV infections (9% vs. 12%), was similar in the everolimus and AZA groups, respectively. The incidence of malignancies was low, and did not show a difference between the everolimus vs. AZA groups (7% vs. 5%).

Use of Everolimus in Liver Transplantation

Efficacy Summary

In study B158 with 119 *de novo* liver transplant patients, the incidence of the composite endpoint (biopsy-proven and treated acute rejection, graft loss, death or lost to follow-up at month 12) was similar for all 3 doses of everolimus (1, 2 and 3 mg/day) and placebo (50%, 43%, 42% and 47%, respectively). No between-group differences were observed for the individual components of this composite endpoint, although there was a trend towards fewer acute rejection episodes and fewer deaths in the everolimus 2 and 4 mg/day groups.

In 119 *de novo* liver transplant patients, the incidence of the composite endpoint (biopsy-proven and treated acute rejection, graft loss, death or lost to follow-up) was similar for all 3 doses of everolimus (1, 2 and 4 mg/day) and placebo at month 12 and for the 3 doses of everolimus at 36 months. There were no dose-related or statistically significant differences between treatment groups in the incidence rate of efficacy failure or its single components. All graft losses and most deaths were secondary to typical post-transplant complications, and none of them were considered to be associated with the study medication. Most efficacy-related events occurred before 12 months. No between-group differences were observed for the individual components of this composite endpoint, although there was a trend towards fewer acute rejection episodes and fewer deaths in the everolimus 2 and 4 mg/day groups though 36 months. Pharmacokinetic modeling, consistent with that observed in renal and cardiac transplant studies suggests that the risk of acute rejection is associated with the trough levels of everolimus similar to other solid transplant organs. Trough levels of everolimus > 3 ng/ml had numerically lower events of rejection within the first year compared to placebo.

Safety Summary
In study B158 with *de novo* liver transplant recipients, more patients in the fixed dose everolimus groups, used with standard doses of cyclosporine, than in the placebo group discontinued study medication due to AEs. The incidence of nonfatal SAEs was slightly higher in the everolimus treated patients. More patients in the everolimus 2 and 4 mg/day groups showed notably high total cholesterol levels. More patients reported hypertriglyceridemia as an AE in the everolimus 2 and 4 mg/day groups than in the other groups. Acute renal failure occurred more frequently in the everolimus 2 and 4 mg/day groups. The incidence of hepatic arterial thrombosis (HAT) was low in this study (2 of 89 patients in the everolimus groups and 1 of 30 patients in the placebo group).

Summary and Conclusions of Novartis' Clinical Data on Everolimus
In summary, Novartis clinical trials demonstrate the safety of therapeutic levels of everolimus greater than 3.0 ng/ml. The blood levels of everolimus achieved with oral doses used in clinical trials of organ transplant rejection greatly exceed the *in vivo* systemic exposure with the implantation of XIENCE V product.

5.4 Packaging Information

Both the XIENCE V RX and OTW systems have a protective sheath that covers the stent/balloon area and is inserted into a dispenser coil. The dispenser coil is placed into an inner header bag, which is heat sealed and given a product label. The header bags are placed into a corrugated shipping box and ethylene oxide (EtO) sterilized.

Post sterilization, each header bag is placed inside an outer foil pouch. First, the foil pouch is purged of ambient air and filled with an inert gas. Next, the pouch is heat sealed, labeled, and placed inside a labeled carton. Individual products in a carton are placed into suitable corrugated boxes designed to protect the packaged product from damage during transit.